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USE OF A PERIODIC VACCINATION STRATEGY TO CONTROL THE SPREAD OF EPIDEMICS WITH SEASONALLY VARYING CONTACT RATE

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Abstract. In this paper, a general periodic vaccination has been applied to control the spread and transmission of an infectious disease with latency. A SEIRS[1] epidemic model with general periodic vaccination strategy is analyzed. We suppose that the contact rate has period T, and the vaccination function has period LT, where L is an integer. Also we apply this strategy in a model with seasonal variation in the contact rate. Both the vaccination strategy and the contact rate are general time-dependent periodic functions. The same SEIRS models have been examined for a mixed vaccination strategy composed of both the time-dependent periodic vaccination strategy and the conventional one. A key parameter of the paper is a conjectured value R_0^c for the basic reproduction number. We prove that the disease-free solution (DFS) is globally asymptotically stable (GAS) when $R_0^{sup} < 1$. If $R_0^{inf} > 1$, then the DFS is unstable, and we prove that there exists a nontrivial periodic solution whose period is the same as that of the vaccination strategy. Some persistence results are also discussed. Necessary and sufficient conditions for the eradication or control of the disease are derived. Threshold conditions for these vaccination strategies to ensure that $R_0^{sup} < 1$ and $R_0^{inf} > 1$ are also investigated.

1. **Introduction.** Mass immunization is frequently used as a tool to control the spread of epidemics. The simplest vaccination strategy is to vaccinate all individuals at a constant rate. This may also be combined with vaccination of a fixed fraction of very young children at the smallest possible age where maternal antibodies no longer confound the effect of the vaccine, commonly 9–18 months for measles. In this paper, we ignore the effect of maternal antibodies, so these young children are in essence vaccinated at birth. In the absence of vaccination, cases of many common childhood diseases show a regular periodic oscillation whose period is a whole number of years [9, 14]. Much work has been done that analyzes seasonal periodic outbreaks of infectious diseases by considering seasonal variation in the contact rate [5, 9, 14].

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[1]See the Appendix for a list of symbols, abbreviations and medical terms used in the paper.

Recently it has been postulated that in some circumstances a periodic vaccination strategy, for example, pulse vaccination, can be a more efficient use of limited immunization resources than a continuous constant vaccination effort [1, 11, 15]. In this paper, we study a general continuous periodic vaccination strategy $r(t)$. This is combined with vaccination of a given proportion of newborn individuals. Because in many real diseases there is a time delay between the time an individual becomes infected and the time he or she becomes infectious, we introduced an exposed or latent class into the model. We consider the model with both a periodic disease transmission rate and a constant one.

If the combined vaccination strategy is applied in the situation where no disease is present, then the number of susceptibles eventually reaches a unique periodic solution. Our results lead us to conjecture that this combined periodic and fixed vaccination strategy is sufficient to eliminate disease from the population exactly when the weighted, time-averaged, disease-free susceptible population is less than a certain threshold value.

1.1. **The pulse vaccination strategy.** Pulse vaccination vaccinates susceptibles at discrete points in time, usually at regular intervals. One such example is the use of annual immunization days, which was successful in eradicating measles from The Gambia between 1967 and 1972 [17]. In recent times, a pulse vaccination strategy has been applied in South and Central America and was highly successful against poliomyelitis [4, 13]. This method is now used in Brazil, where it is both easier to arrange and has a greater uptake than the conventional continuous vaccination strategy. Pulse vaccination has been used in Africa recently albeit with only partial success. Agur et al. [1] discuss the possibility of implementation of the pulse vaccination method in Israel.

Pulse vaccination has also been used in the United Kingdom. In November 1994, a single dose of combined measles and rubella (MR) vaccine was given to children aged 5 to 16 years. In England and Wales, an average of 92% of these children were vaccinated. This policy caused a significant fall in the number of cases of measles reported to the Office of Population Censuses and Surveys. It was concluded that the application of pulse immunization to all schoolchildren would probably prevent a large rate of morbidity and mortality and would have a marked effect on measles transmission for several years [11].

Nokes and Swinton [11] use simple steady-state and age-structured dynamic models to extend the theory of the mechanism of action of pulse vaccination, and to explore the relationship between the maximum permitted interval between pulses and key epidemiological, demographic, and vaccination variables. They further developed the work of Agur et al. [1]. An ordinary differential equation model is used to derive equilibrium expressions for the pulse interval and considers combined routine and pulse vaccination. Simulations using age-structured compartmental deterministic models illustrate complex epidemiological dynamics associated with pulse vaccination, particularly when there is age heterogeneity in contact rates in the population.

Pulse vaccination in an SIR epidemic model with vaccination has been considered by Shulgin et al. [15]. They consider a vaccination function $r(t) = \sum_{n=0}^{\infty} p\delta(t-nT)$. Here, $\delta(t)$ is the Dirac delta function, and p is a constant. This corresponds to a series of pulse vaccinations, each separated by time T. They found that a periodic DFS is possible where the numbers of susceptibles and recovereds are periodic functions with a period equal to that of the pulse vaccination. Shulgin et al. also

discovered a threshold condition for this periodic infection-free solution to be locally stable, first in the case where β, the transmission rate of the infection, is a constant, and second in the more general case where the disease transmission rate $\beta(t)$ is a nonconstant periodic function with the same period T as $r(t)$. If this threshold is not exceeded, then the periodic DFS is locally stable and a serious epidemic will not occur. In what follows, we investigate a more realistic and complicated SEIRS model with a general continuous periodic vaccination rate $r(t)$.

2. **The SEIRS model with vaccination.** Our SEIRS model of the spread of infectious diseases makes the following assumptions:

1. The total population size is N, and the per capita birth rate is a constant μ. As births balance deaths, we must have that the per capita death rate is also μ.
2. The population is uniform and mixes homogeneously.
3. The population is divided into susceptible, exposed, infective, and recovered individuals. The total number of individuals in each of these classes is $S \equiv S(t),\ E \equiv E(t),\ I \equiv I(t)$, and $R \equiv R(t)$, respectively.
4. The infection rate $\beta(t)$ is defined as the total rate at which potentially infectious contacts occur between two individuals. A potentially infectious contact is one which will transmit the disease if one individual is susceptible and the other is infectious, so the total rate at which susceptibles become exposed is $\beta(t)SI$. Biological considerations mean that $\beta(t)$ is continuous. We also assume that either (i) $\beta(t)$ is not identically zero, positive, nonconstant and periodic of period T or (ii) $\beta(t) = \beta$ is a constant.
5. The susceptibles move from the exposed class to the infective class at a constant rate σ, where $(1/\sigma)$ is the average latent period conditional on survival to the end of it.
6. The infectives move from the infective class to the recovered class at a constant rate γ, where $(1/\gamma)$ is the average infectious period conditional on survival to the end of it. We assume that the disease does not give permanent immunity, so individuals transfer back from the immune to the susceptible class at a constant per capita rate δ.
7. A fraction p $(0 \leq p \leq 1)$ of all newborn children are vaccinated. In addition all susceptibles in the population are vaccinated at a time-dependent periodic rate $r(t)$. This is the periodic vaccination strategy. We shall suppose that $r(t)$ is periodic with period LT. The case where $r(t)$ has period T can be obtained by setting $L = 1$.

Our SEIRS model with time-dependent vaccination strategy can be written as a set of four coupled nonlinear ordinary differential equations as:

$$\frac{dS}{dt} = \mu N(1-p) - \beta(t)SI - (\mu + r(t))S + \delta R, \tag{1}$$

$$\frac{dE}{dt} = \beta(t)SI - (\mu + \sigma)E, \tag{2}$$

$$\frac{dI}{dt} = \sigma E - (\mu + \gamma)I, \tag{3}$$

$$\frac{dR}{dt} = \mu N p + r(t)S + \gamma I - (\mu + \delta)R, \tag{4}$$

with

$$S + E + I + R = N. \tag{5}$$

Here the disease transmission rate $\beta(t)$ and the vaccination rate $r(t)$ are nonzero, positive, continuous periodic functions. The system (1)–(5) has no equilibrium points, but a DFS, with $E(t) = I(t) = 0$, is still possible.

Consider the region D in $\mathcal{R}^4$, defined by

$$D = \{(S, E, I, R) \in [0, N]^4 \mid S + E + I + R = N\}.$$

The system of differential equations (1)–(4) with initial conditions in D obviously starts off in the region D. The right-hand sides of these equations are differentiable with respect to S, E, I, and R with continuous derivatives. It is straightforward to show using standard techniques [7] (and considering separately the cases $E(0) = I(0) = 0$ and $E(0) > 0$ or $I(0) > 0$) that the equations (1)–(4) with initial conditions in D have a unique solution that remains in D for all time and moreover,

$$S + E + I + R = N.$$

3. **The DFS.** When $r(t)$ is a nonconstant bounded continuous periodic function, there is no equilibrium point for the system (1)–(5). So there is no disease-free equilibrium point; however, a periodic DFS corresponding to the case $E(t) = I(t) = 0$. In this case, (1) becomes

$$\begin{aligned} \frac{dS}{dt} &= \mu N(1-p) - (\mu + r(t))S + \delta R, \\ &= N(\mu(1-p) + \delta) - (\mu + r(t) + \delta)S. \end{aligned} \tag{6}$$

If $E(t) = I(t) = 0$, (6) has a solution for $S(t)$. We examine the behavior of this solution. Integrating (6), we find that

$$\begin{aligned} S(t) &= S(t_0) \exp\left[-(\mu+\delta)(t-t_0) - \int_{t_0}^{t} r(\tau)d\tau\right] \\ &+ N[\mu(1-p)+\delta] \exp\left[-(\mu+\delta)(t-t_0) - \int_{t_0}^{t} r(\tau)d\tau\right] \\ &\int_{t_0}^{t} \exp\left[(\mu+\delta)(\zeta - t_0) + \int_{t_0}^{\zeta} r(\tau)d\tau\right] d\zeta. \end{aligned} \tag{7}$$

Hence,

$$\begin{aligned} S(t_0+(n+1)LT) &= S(t_0+nLT)\exp\left[-(\mu+\delta)LT-\int_{t_0}^{t_0+LT} r(\tau)d\tau\right] \\ &+ N[\mu(1-p)+\delta]\exp\left[-(\mu+\delta)LT-\int_{t_0}^{t_0+LT} r(\tau)d\tau\right] \\ &\int_{t_0}^{t_0+LT}\exp\left[(\mu+\delta)(\zeta-t_0)+\int_{t_0}^{\zeta} r(\tau)d\tau\right]d\zeta. \end{aligned} \tag{8}$$

Equation (8) gives a recursive relationship between the number of susceptibles at time t_0+nLT, $n=1,\ 2,\ 3,\ \ldots$. If we let $S_n=S(t_0+nLT)$, then (8) defines a mapping F such that

$$F(S_n)=S_{n+1}.$$

If S_1 and S_2 are different values of S, then

$$|F(S_1)-F(S_2)|\le|S_1-S_2|\exp(-\mu LT).$$

So, F is a contraction mapping [3] and has a unique fixed point $S^*(t_0)$ such that

$$\begin{aligned} S^*(t_0) &= \left(N[\mu(1-p)+\delta]\exp\left[-(\mu+\delta)LT-\int_0^{LT} r(\tau)d\tau\right]\right. \\ &\left.\int_{t_0}^{t_0+LT}\exp\left[(\mu+\delta)(\zeta-t_0)+\int_{t_0}^{\zeta} r(\tau)d\tau\right]d\zeta\right) \\ &\frac{1}{1-\exp\left[-(\mu+\delta)LT-\int_0^{LT} r(\tau)d\tau\right]}. \end{aligned} \tag{9}$$

Hence, $S^*(t_0+LT)=S^*(t_0)$. So, S^* is a periodic function of t. Differentiating (9), $S^*(t_0)$ is continuously differentiable with respect to t_0 and $\hat{S}(t)=S^*(t)$, $\hat{E}=\hat{I}=0$, and $\hat{R}(t)=R^*(t)=N-S^*(t)$ is a disease-free periodic solution of the system (1)–(5), which repeats itself every LT years. We have the following result.

THEOREM 3.1. *Equations (1)–(5) have a disease-free periodic solution of period LT that is continuously differentiable, and this is the only disease-free periodic solution to (1)–(5); any disease-free solution to (1)–(5) approaches this one as time becomes large.*

Proof This is a straightforward adaption of the SIRS model considered in [10] for the case $L=1$. □

Recall that R_0, the basic reproduction number of the disease, is defined as the expected number of secondary cases caused by a single infected case entering the disease-free population at equilibrium [2]. Anderson and May [2] call this the basic reproduction rate, but it is a number, not a rate. Consider a single newly infected person entering the population at the DFS. During the latent period, this person faces a death rate μ and leaves for the infectious class at rate σ. Assuming that the time taken for these two events to happen follow independent exponential distributions, the probability that the individual survives his or her incubation period is $\sigma/(\mu+\sigma)$. Similarly, the average length of the infectious period is $\tau=1/(\mu+\gamma)$. The average value taken over a cycle of the expected number of secondary

cases produced by a single infected person entering the population at the DFS is our conjectured value for R_0; namely,

$$R_0^c = \frac{1}{LT}\int_0^{LT} \frac{\sigma\beta(\tau)\hat{S}(\tau)d\tau}{(\mu+\sigma)(\mu+\gamma)}. \tag{10}$$

Define $R_0^{sup} =$

$$\frac{\sigma}{(\mu+\gamma)(\mu+\sigma)} \sup_{t\in[0,LT]} \int_0^{LT} \frac{(\mu+\sigma)\beta(t-\zeta)\hat{S}(t-\zeta)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]}, \tag{11}$$

and $R_0^{inf} =$

$$\frac{\sigma}{(\mu+\gamma)(\mu+\sigma)} \inf_{t\in[0,LT]} \int_0^{LT} \frac{(\mu+\sigma)\beta(t-\zeta)\hat{S}(t-\zeta)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]}. \tag{12}$$

Later we show that $R_0^{sup} \geq R_0^c \geq R_0^{inf}$, with both of the inequalities being strict if $\beta(t)\hat{S}(t)$ is nonconstant on $[0, LT]$. We expect that if $R_0^c > 1$ the disease will take off, whereas if $R_0^c \leq 1$ the disease will die out. However, we have been able to show only that if $R_0^{sup} < 1$ the disease will die out, and if $R_0^{inf} > 1$, then the disease will take off if it is initially present. In the following sections, we formally investigate these results.

4. **The stability analysis of the DFS.** In this section we concentrate on the stability analysis of the DFS, and we try to extend the results obtained in [6] for an SIRS model with constant vaccination of individuals of all ages.

4.1. **Stability of the DFS when $\mathbf{R_0^{sup} < 1}$.** Our first result is to show that the DFS $(\hat{S}(t), 0, 0, \hat{R}(t))$ is GAS when $R_0^{sup} < 1$. We need the following lemma.

LEMMA 4.1.

$$\limsup_{t\to\infty}(S-\hat{S})(t) \leq 0.$$

Proof From equation (1),

$$\begin{aligned} \frac{dS}{dt} &= \mu N(1-p) - \beta(t)SI - (\mu + r(t))S + \delta R, \\ &\leq N(\mu(1-p)+\delta) - (\mu + r(t) + \delta)S. \end{aligned}$$

As $(\hat{S}(t), 0, 0, \hat{R}(t))$ is a solution of (1), then

$$\frac{d\hat{S}}{dt} = N(\mu(1-p)+\delta) - (\mu + r(t) + \delta)\hat{S}.$$

Therefore,

$$\frac{d(S-\hat{S})}{dt} \leq -(\mu + r(t) + \delta)(S-\hat{S}).$$

Integrating this inequality we find that

$$(S-\hat{S})(t) \leq (S-\hat{S})(t_0)\exp\left(-(\mu+\delta)(t-t_0) - \int_{t_0}^{t} r(\tau)d\tau\right).$$

Lemma 4.1 now follows. □

Now we can prove the global stability of the DFS when $R_0^{sup} < 1$.

THEOREM 4.1. *If $R_0^{sup} < 1$, the DFS $(\hat{S}, 0, 0, \hat{R})$ is GAS for the system (1)–(5).*

Proof Since

$$\frac{dI}{dt} = \sigma E - (\mu + \gamma)I,$$

we can easily show that,

$$I^\infty \leq \frac{\sigma E^\infty}{\mu + \gamma}.$$

The idea behind the proof of Theorem 4.1 is as follows: By Lemma 4.1, we know that given $\epsilon > 0$, there exists t_1 such that $S(t) \leq \hat{S}(t) + \epsilon$ and $I \leq I^\infty + \epsilon$ for all $t \geq t_1$. From (2), we bound $E(t)$ above and from this upper bound, we deduce that $E^\infty = 0$. Suppose that $E^\infty > 0$. Integrating (2), we find that for $t \geq t_0 > t_1$,

$$\begin{aligned} E(t) &\leq E(t_0)\exp[-(\mu+\sigma)(t-t_0)] \\ &+ (I^\infty + \epsilon)\exp[-(\mu+\sigma)t]\int_{t_0}^{t} \beta(\tau)(\hat{S}(\tau)+\epsilon)\exp[(\mu+\sigma)\tau]d\tau. \end{aligned}$$

Define $y(\tau) = \beta(\tau)\hat{S}(\tau)$. Note that $y(\tau)$ is a nonzero positive periodic function with period LT, so

$$\exp[-(\mu+\sigma)t]\int_{t_0}^{t} y(\tau)\exp[(\mu+\sigma)\tau]d\tau = \int_0^{t-t_0} y(t-u)\exp[-(\mu+\sigma)u]du.$$

Suppose that $(k+1)LT \geq t - t_0 \geq kLT$. We have that

$$\begin{aligned} &\int_0^{t-t_0} y(t-u)\exp[-(\mu+\sigma)u]du \\ &\qquad = \int_0^{LT} y(t-u)\exp[-(\mu+\sigma)u]du\Big(1+\exp[-(\mu+\sigma)LT] \\ &\qquad + \exp[-(\mu+\sigma)2LT] + \cdots + \exp[-(\mu+\sigma)(k-1)LT]\Big) \\ &\qquad + \int_{kLT}^{t-t_0} y(t-u)\exp[-(\mu+\sigma)u]du, \\ &\qquad \leq \int_0^{LT} y(t-u)\exp[-(\mu+\sigma)u]du\Big(1+\exp[-(\mu+\sigma)LT] \\ &\qquad + \exp[-(\mu+\sigma)2LT] + \cdots + \exp[-(\mu+\sigma)kLT]\Big), \\ &\qquad < \int_0^{LT} \frac{y(t-\zeta)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]}. \end{aligned}$$

Therefore, for $t \geq t_0$ we find that

$$\begin{aligned} E(t) &\leq E(t_0)\exp[-(\mu+\sigma)(t-t_0)] \\ &+ \frac{I^\infty+\epsilon}{\mu+\sigma}\int_0^{LT} \frac{(\mu+\sigma)\beta(t-\zeta)(\hat{S}(t-\zeta)+\epsilon)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]}, \\ &\leq N\exp[-(\mu+\sigma)(t-t_0)] \\ &+ \frac{I^\infty+\epsilon}{\mu+\sigma}\left(\sup_{t\in[0,LT]}\int_0^{LT} \frac{(\mu+\sigma)y(t-\zeta)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]}\right. \\ &+ \left.\epsilon\int_0^{LT} \frac{(\mu+\sigma)\beta(t-\zeta)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]}\right). \end{aligned}$$

Now choose $t_2 > t_0$ large enough so that for $t \geq t_2$, $N \exp[-(\mu+\sigma)(t-t_0)] < \epsilon$. Then for $t \geq t_2$,

$$E(t) \leq$$
$$R_0^{sup} E^\infty + \epsilon \left(1 + \sup_{t\in[0,LT]} \int_0^{LT} \frac{y(t-\zeta)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]} + \left(\frac{I^\infty+\epsilon}{\mu+\sigma}\right)\beta_{max} \right),$$

where $\beta_{max} = \sup_{u\in[0,LT]} \beta(u)$. Now choose ϵ small enough so that

$$\epsilon \left(1 + \sup_{t\in[0,LT]} \int_0^{LT} \frac{y(t-\zeta)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]} + \left(\frac{I^\infty+\epsilon}{\mu+\sigma}\right)\beta_{max} \right) < \psi E^\infty,$$

where $R_0^{sup} + \psi < 1$ and $\psi > 0$. Hence for $t \geq t_2$, we have that $E(t) \leq (R_0^{sup}+\psi)E^\infty$. Thus, $0 \leq E^\infty \leq (R_0^{sup}+\psi)E^\infty$. So, $E^\infty = 0$. Hence also $I^\infty = 0$ and $E(t) \to 0$ and $I(t) \to 0$ as $t \to \infty$. It remains to show that $(S-\hat{S})(t) \to 0$ and $(R-\hat{R})(t) \to 0$ as $t \to 0$. Because $\hat{R}(t)$ is a solution of equation (4) when $E(t) = I(t) = 0$, we have that,

$$\frac{d(R-\hat{R})}{dt} = r(t)(S-\hat{S}) + \gamma I - (\mu+\delta)(R-\hat{R}). \tag{13}$$

Given $\epsilon_1 > 0$ using Lemma 4.1, there exists t_3 such that $E(t) + I(t) \leq \epsilon_1$ and $S(t) \leq \hat{S}(t) + \epsilon_1$ for all $t \geq t_3$. So for $t \geq t_3$,

$$\frac{d(R-\hat{R})}{dt} \leq (r_{max}+\gamma)\epsilon_1 - (\mu+\delta)(R-\hat{R}),$$

where $r_{max} = \sup_{u\in[0,LT]} r(u)$. Integrating this inequality, we find that

$$\begin{aligned}(R-\hat{R})(t) &\leq (R-\hat{R})(t_3)\exp[-(\mu+\delta)(t-t_3)] \\ &+ \epsilon_1 \left(\frac{r_{max}+\gamma}{\mu+\delta}\right)(1-\exp[-(\mu+\delta)(t-t_3)]), \\ &\leq N\exp[-(\mu+\delta)(t-t_3)] + \epsilon_1\left(\frac{r_{max}+\gamma}{\mu+\delta}\right).\end{aligned}$$

It is now straightforward to show that given $\epsilon_2 > 0$, there exists t_4 such that $R(t)-\hat{R}(t) \leq \epsilon_2$ for $t \geq t_4$. Hence, $S(t) = N-R(t)-I(t)-E(t) \geq N-\hat{R}(t)-\epsilon_1-\epsilon_2$ for $t \geq t_4$. Using Lemma 4.1, we deduce that $S(t) \to \hat{S}(t)$ as $t \to \infty$. Since $R(t) = N - S(t) - I(t) - E(t)$, then we must have that $R(t) \to N - \hat{S}(t) = \hat{R}(t)$ at $t \to \infty$. This completes the proof of Theorem 4.1. □

Thus if $R_0^{sup} < 1$, the DFS is GAS.

5. **The existence of periodic solutions.** The existence of a periodic solution of (1)–(5) can be proved in two stages. The first is that if $R_0^{inf} > 1$, then there exists a minimum threshold value for $I(t)$ such that if $I(0) > 0$ or $E(0) > 0$, then $I(t)$ will rise above this threshold value, and from then on the time spent continuously beneath it can be bounded above by a bound that depends only on the model parameters, not on the initial conditions. Moreover, the time taken to rise initially above the threshold can be bounded above by a bound that depends only on the initial value $I(0)$ and the model parameters.

In the second stage, by using fixed-point theory we prove that the system (1)–(5) has an LT-periodic solution. These results are also true for the same model

when the contact rate is constant if the vaccination strategy is a general continuous periodic function.

To prove the existence of periodic solutions of (1)–(5), we need the following notations.

DEFINITION 5.1.

$$\bar{R}_0^{inf}(\lambda) = \frac{\sigma}{(\mu+\gamma)(\mu+\sigma)} \inf_{t\in[0,LT]} \int_0^{LT} \frac{(\mu+\sigma)y(t-\zeta)\exp[-(\mu+\sigma+\lambda)\zeta]d\zeta}{1-\exp[-(\mu+\sigma+\lambda)LT]}.$$

Define

$$f(t,\lambda) = \int_0^{LT} \frac{y(t-u)\exp[-(\mu+\sigma+\lambda)u]}{1-\exp[-(\mu+\sigma+\lambda)LT]}du.$$

Note that $f(t,\lambda)$ is monotone decreasing in λ for a fixed t, and hence, $\bar{R}_0^{inf}(\lambda)$ is monotone decreasing in λ.

Now consider the equation $\lambda^2 + d_1\lambda + d_2(\lambda) = 0$, where

$$d_1 = (\mu+\sigma) + (\mu+\gamma) \qquad \text{and} \qquad d_2(\lambda) = \frac{1}{2}(1-\bar{R}_0^{inf}(\lambda))(\mu+\sigma)(\mu+\gamma).$$

If $\bar{R}_0^{inf}(0) = R_0^{inf} > 1$, then $d_2(0) < 0$ and the equation $\lambda^2 + d_1\lambda + d_2(\lambda) = 0$ has a unique positive root, say $\lambda_1 > 0$. Then

$$\frac{(\bar{R}_0^{inf}(\lambda_1)+1)(\mu+\sigma)(\mu+\gamma)}{2(\mu+\sigma+\lambda_1)(\mu+\gamma+\lambda_1)} = 1. \tag{14}$$

DEFINITION 5.2.

$$\bar{\beta}_{sup} = \sup_{t\in[0,LT]} \int_0^{LT} \frac{(\mu+\sigma)\beta(t-\zeta)\exp[-(\mu+\sigma+\lambda_1)\zeta]d\zeta}{1-\exp[-(\mu+\sigma+\lambda_1)LT]}.$$

DEFINITION 5.3.

$$K_1(\eta) = \frac{\frac{1}{4}(\bar{R}_0^{inf}(\lambda_1)-1)(\mu+\sigma)(\mu+\gamma)(1-\eta)}{\left[1+\frac{\beta_{max}N}{(\mu+\sigma)}+\frac{2\gamma}{(\mu+\delta)}\right]\sigma\bar{\beta}_{sup}},$$

where $\eta < 1$ is an arbitrarily small positive number and $\psi(\eta)$ is a positive number such that

$$0 < \psi(\eta) < \min\left\{\frac{K_1(\eta)}{2}, N\left[1-\frac{\beta_{max}\epsilon_0(\eta)}{(\mu+\sigma)}\right], N-\frac{2\gamma\epsilon_0(\eta)}{(\mu+\delta)}\right\},$$

where $\epsilon_0(\eta)$ is a positive number such that

$$0 < \epsilon_0(\eta) < \min\left\{\frac{(\mu+\sigma)}{\beta_{max}}, \frac{N(\mu+\delta)}{2\gamma}, K_1(\eta)\right\}.$$

Here $K_1(\eta)$ is a well-defined positive number, and $\epsilon_0(\eta)$ and $\psi(\eta)$ are in well-defined ranges. Given $\eta > 0$, we suppose that $I(0) > 0$ and find an upper bound for the time for which $I(t)$ can spend continuously beneath $\epsilon_0(\eta)$. We do this by supposing that $I(t)$ remains indefinitely and continuously beneath $\epsilon_0(\eta)$, and we deduce a contradiction. For the moment, we suppose that $\eta > 0$ is fixed and write K_1, ϵ_0, and ψ for $K_1(\eta)$, $\epsilon_0(\eta)$, and $\psi(\eta)$ respectively. We need four preliminary lemmas. We use these to show that $I(t)$ must eventually rise again above ϵ_0, and

the time taken to do this can be bounded above by a time depending only on ϵ_0, ψ, and the model parameters.

If the solution has the initial value $I(0) > \epsilon_0$, suppose that the solution $I(t)$ drops beneath ϵ_0 for the first time at time ζ_0. Then, without loss of generality, we can assume that $\zeta_0 = 0$. Our first result is that $E(t)$ also becomes small.

LEMMA 5.1. *Suppose that $I(0) = \epsilon_0$ and $I(t) \leq \epsilon_0$ for all $t \geq 0$. Then there exists a time $T_0 > 0$ such that $E(t) < \dfrac{\beta_{max} N \epsilon_0}{(\mu + \sigma)} + \psi$ for all $t > T_0$, where T_0 depends only on ψ, ϵ_0, and the model parameters.*

Proof This is straightforward. □

LEMMA 5.2. *Suppose that $I(t) \leq \epsilon_0$ for all t. Then there exists a time $T_1 > 0$ such that*

$$R(t) \;\leq\; \hat{R}(t) + \frac{2\gamma\epsilon_0}{\mu + \delta} + \psi$$

for all $t > T_1$, and T_1 depends only on ψ, ϵ_0, and the model parameters.

Proof Given $\epsilon > 0$, there exists t_0, depending only on ϵ and the model parameters, such that $(S - \hat{S})(t) \leq \epsilon$ for all $t \geq t_0$. So for $t > t_0$ from (13),

$$\frac{d(R - \hat{R})}{dt} \;\leq\; r_{max}\epsilon + \gamma\epsilon_0 - (\mu + \delta)(R - \hat{R}).$$

Lemma 5.2 now follows straightforwardly. □

Now, supposing that $I(0) = \epsilon_0$, our next aim is to find a time T_2 and a strictly positive lower bound E_1 for $E(T_2)$, where E_1 and T_2 depend only on the model parameters and ϵ_0. We deal with the two cases, $p < 1$ and $p = 1$, separately in the following two lemmas.

LEMMA 5.3. *If $p < 1$, define a time $T_2 = (x+1)LT$, where x is the smallest integer such that $xLT \geq T_3 = (\ln 2)/(\beta_{max}N + \mu + r_{max})$ and $E_1 = E_2 \exp[-(\mu + \sigma)T_2] > 0$, where $E_2 = \epsilon_0 S_1 \int_0^{LT} \beta(\tau) \exp[-\gamma\tau] d\tau \; \exp[-\gamma x LT] > 0$ and $S_1 = \mu N(1 - p)/2(\beta_{max}N + \mu + r_{max})$. Then $E(T_2) \geq E_1 > 0$, and E_1 and T_2 depend only on the model parameters and ϵ_0.*

Proof From (1), we have that

$$\frac{dS}{dt} \;\geq\; \mu N(1 - p) - (\beta_{max}N + \mu + r_{max})S.$$

Integrating this inequality, we have that

$$S(t) \;\geq\; \frac{\mu N(1 - p)}{\beta_{max}N + \mu + r_{max}} \left(1 - \exp[-(\beta_{max}N + \mu + r_{max})t]\right).$$

As $I(0) = \epsilon_0$, $I(t) \geq \exp[-(\mu + \gamma)t]$. Hence for $t \geq T_3$,

$$\frac{dE}{dt} + (\mu + \sigma)E \;\geq\; \beta(t) S_1 \epsilon_0 \exp[-(\mu + \gamma)t].$$

Multiplying by $\exp[(\mu + \sigma)t]$ and integrating between xLT and $(x + 1)LT$, the required result follows. □

LEMMA 5.4. *If $p = 1$, define a time $T_2 = (x_1+1)LT$, where x_1 is the smallest integer such that $x_1 LT \geq T_4 + T_5$. Here $T_4 = (\ln 2)/(\mu + \delta)$ and $T_5 = (\ln 2)/(\beta_{max}N + \mu + r_{max})$. Define $E_1 = E_3 \exp[-(\mu+\sigma)T_4] > 0$, $E_3 = \epsilon_0 S_2 \int_0^{LT} \beta(\tau)\exp[-\gamma\tau]d\tau \exp[-\gamma x_1 LT] > 0$, $S_2 = (\delta R_1)/(2(\beta_{max}N + \mu + r_{max}))$, and $R_1 = (\mu N)/2(\mu+\delta)$. Then $E(T_2) \geq E_1 > 0$, and T_2 and E_1 depend only on the model parameters and ϵ_0.*

Proof From equation (4), we have that

$$\frac{dR}{dt} \geq \mu N p - (\mu+\delta)R.$$

Integrating this inequality and arguing similarly to Lemmas 5.2 and 5.3, we deduce that for $t \geq T_4 = (\ln 2)/(\mu+\delta)$, $R(t) \geq (\mu N)/(2(\mu+\delta)) = R_1$. Again, from (1), we have that for $t \geq T_4$,

$$\frac{dS}{dt} \geq \delta R_1 - (\beta_{max}N + \mu + r_{max})S.$$

Integrating this inequality for $t \geq T_4$, we have that

$$S(t) \geq \frac{\delta R_1}{\beta_{max}N + \mu + r_{max}} \left(1 - \exp[-(\beta_{max}N + \mu + r_{max})(t - T_4)]\right).$$

Hence for $t \geq T_4 + T_5$, $S(t) \geq S_2$, and

$$\frac{dE}{dt} + (\mu+\sigma)E \geq \beta(t) S_2 I.$$

Lemma 5.4 is now a straightforward argument as in Lemma 5.3. □

These results allow us to proceed to the first theorem in this section, which gives a lower bound η_0 for I_∞ and an upper bound on the initial time for which the value of $I(t)$ remains beneath η_0.

THEOREM 5.1. *If $R_0^{inf} > 1$, then there exists $\eta_0 > 0$ such that all $\eta_1 > 0$; if $I(0) \geq \eta_1$, then $I(t) \geq \eta_0$ for all $t \geq T(\eta_1)$, where $T(\eta_1)$ depends only on η_1 and the model parameters.*

Proof First, suppose that $I(0) = \epsilon_0$ and $I(t) \leq \epsilon_0$ for $t \geq 0$. We show that $R_0^{inf} > 1$ forces $I(t)$ to rise to at least the level ϵ_0 by a time $\tilde{T}$ that depends only on ψ, ϵ_0, and the model parameters. From Lemmas 5.1 and 5.2, we have shown that for $t > T_6 = \max(T_0, T_1)$,

$$\begin{aligned} S(t) &= N - E(t) - I(t) - R(t), \\ &\geq \left[\hat{S}(t) - 2\psi - \epsilon_0\left(1 + \frac{\beta_{max}N}{(\mu+\sigma)} + \frac{2\gamma}{(\mu+\delta)}\right)\right]. \end{aligned}$$

By Definition 5.3, we have that

$$\begin{aligned} 2\psi + \epsilon_0 &\left[1 + \frac{\beta_{max}N}{(\mu+\sigma)} + \frac{2\gamma}{(\mu+\delta)}\right] \\ &< K_1\left[2 + \frac{\beta_{max}N}{(\mu+\sigma)} + \frac{2\gamma}{(\mu+\delta)}\right], \qquad \text{as } \psi < (K_1/2) \text{ and } \epsilon_0 < K_1, \\ &< K_1 + \frac{\frac{1}{4}(\bar{R}_0^{inf}(\lambda_1) - 1)(\mu+\sigma)(\mu+\gamma)(1-\eta)}{\sigma\bar{\beta}_{sup}}, \quad \text{using Definition 5.3}, \\ &< \frac{(\bar{R}_0^{inf}(\lambda_1) - 1)(\mu+\sigma)(\mu+\gamma)(1-\eta)}{2\sigma\bar{\beta}_{sup}}. \end{aligned} \tag{15}$$

From (2), choose $t_0 > T_7 = \max(T_4, T_6)$, then $E(t_0) \geq E_1 \exp[-(\mu+\sigma)(t_0-T_4)] > 0$, using Lemmas 5.3 and 5.4, and from (3), we have that $I(t_0) \geq \epsilon_0 \exp[-(\mu+\gamma)t_0] > 0$. Note that from Definition 5.1 we have that

$$\bar{R}_0^{inf}(\lambda) = \frac{\sigma}{(\mu+\gamma)(\mu+\sigma)} \inf_{t\in[0,LT]} \int_0^{LT} \frac{(\mu+\sigma)y(t-\zeta)\exp[-(\mu+\sigma+\lambda)\zeta]d\zeta}{1-\exp[-(\mu+\sigma+\lambda)LT]}.$$

Given a small enough $\eta > 0$, choose ϵ_1 and an integer k so that

$$\frac{\sigma}{(\mu+\gamma)(\mu+\sigma)} \inf_{t\in[0,LT]} \int_0^{LT} (\mu+\sigma)y(t-\zeta)\exp[-(\mu+\sigma+\lambda_1)\zeta]d\zeta$$
$$\left(1+\exp[-(\mu+\sigma+\lambda_1)LT] + \exp[-(\mu+\sigma+\lambda_1)2LT] + \cdots \right.$$
$$\left. + \exp[-(\mu+\sigma+\lambda_1)(k-1)LT]\right) > \bar{R}_0^{inf}(\lambda_1)(1-\eta), \tag{16}$$

$$\text{and} \quad 0 < \epsilon_1 < \min\left\{\frac{\epsilon_0}{2}\exp[-(\mu+\gamma)(t_0+kLT)],\right.$$
$$\left.\frac{\sigma}{2(\mu+\gamma+\lambda_1)}E_1\exp[-(\mu+\sigma)(t_0-T_4+kLT)]\right\}.$$

Then $E(t_0) \geq 2\epsilon_1((\mu+\gamma+\lambda_1)/\sigma)$ and $I(t_0) \geq 2\epsilon_1$. Provided that $I(t)$ remains continuously below the level ϵ_0,

$$I(t_0+\tau) \geq \epsilon_1\exp[\lambda_1(\tau-kLT)] \quad \text{and} \quad E(t_0+\tau) \geq \frac{\mu+\gamma+\lambda_1}{\sigma}\epsilon_1\exp[\lambda_1(\tau-kLT)].$$

Define τ_0 such that

$$\tau_0 \quad = \quad \inf\left\{\xi \geq 0 : I(t_0+\tau) \geq \epsilon_1\exp[\lambda_1(\tau-kLT)] \text{ and}\right.$$
$$\left. E(t_0+\tau) \geq \frac{\mu+\gamma+\lambda_1}{\sigma}\epsilon_1\exp[\lambda_1(\tau-kLT)] \quad \text{for} \quad \tau\in[0,\xi]\right\}.$$

By continuity, $\tau_0 > 0$, and if $\tau_0 < \infty$, then either

$$I(t_0+\tau_0) = \epsilon_1\exp[\lambda_1(\tau_0-kLT)] \text{ or } E(t_0+\tau_0) = \frac{(\mu+\gamma+\lambda_1)}{\sigma}\epsilon_1\exp[\lambda_1(\tau_0-kLT)]. \tag{17}$$

We show that (17) leads to a contradiction. If $\tau_0 \leq kLT$, we have that

$$\begin{aligned} I(t_0+\tau_0) &\geq \epsilon_0\exp[-(\mu+\gamma)(t_0+\tau_0)], \\ &> \epsilon_1\exp[\lambda_1(\tau_0-kLT)], \end{aligned}$$

and

$$\begin{aligned} E(t_0+\tau_0) &\geq E_1\exp[-(\mu+\sigma)(t_0-T_4+\tau_0)], \\ &> \frac{(\mu+\gamma+\lambda_1)\epsilon_1}{\sigma}\exp[\lambda_1(\tau_0-kLT)]. \end{aligned}$$

If $\tau_0 > kLT$ from (3) we have that

$$\begin{aligned} I(t_0+\tau_0) &= I(t_0)\exp[-(\mu+\gamma)\tau_0] \\ &+ \exp[-(\mu+\gamma)(t_0+\tau_0)]\int_{t_0}^{t_0+\tau_0}\sigma E(\zeta)\exp[(\mu+\gamma)\zeta]d\zeta, \\ &> \epsilon_1\exp[\lambda_1(\tau_0-kLT)]. \end{aligned} \tag{18}$$

Also, for $\tau_0 > kLT$, we have that

$$\begin{aligned} E(t_0+\tau_0) = {} & E(t_0)\exp[-(\mu+\sigma)\tau_0] \\ &+ \exp[-(\mu+\sigma)(t_0+\tau_0)]\int_{t_0}^{t_0+\tau_0}\beta(\zeta)S(\zeta)I(\zeta)\exp[(\mu+\sigma)\zeta]d\zeta, \\ &\geq E(t_0)\exp[-(\mu+\sigma)\tau_0]+\epsilon_1\exp[-(\mu+\sigma)(t_0+\tau_0)] \\ &\qquad \int_{t_0}^{t_0+\tau_0}\beta(\zeta)\left(\hat{S}(\zeta)-\frac{(\bar{R}_0^{inf}(\lambda_1)-1)(\mu+\gamma)(\mu+\sigma)(1-\eta)}{2\sigma\bar{\beta}_{sup}}\right) \\ &\qquad \exp[(\mu+\sigma)\zeta+\lambda_1(\zeta-t_0-kLT)]d\zeta, \\ &> \frac{\mu+\gamma+\lambda_1}{\sigma}\epsilon_1\exp[-(\mu+\sigma)\tau_0]+\epsilon_1\exp[\lambda_1(\tau_0-kLT)] \\ &\qquad \int_{t_0}^{t_0+\tau_0}\beta(\zeta)\left(\hat{S}(\zeta)-\frac{(\bar{R}_0^{inf}(\lambda_1)-1)(\mu+\gamma)(\mu+\sigma)(1-\eta)}{2\sigma\bar{\beta}_{sup}}\right) \\ &\qquad \exp[(\mu+\sigma+\lambda_1)(\zeta-t_0-\tau_0)]d\zeta, \\ &> \epsilon_1\exp[\lambda_1(\tau_0-kLT)]\int_0^{\tau_0}\beta(t_0+\tau_0-u)\left(\hat{S}(t_0+\tau_0-u)\right. \\ &\qquad \left.-\frac{(\bar{R}_0^{inf}(\lambda_1)-1)(\mu+\gamma)(\mu+\sigma)(1-\eta)}{2\sigma\bar{\beta}_{sup}}\right)\exp[-(\mu+\sigma+\lambda_1)u]du, \\ &> \left(\frac{\mu+\gamma}{\sigma}\bar{R}_0^{inf}(\lambda_1)(1-\eta)-\frac{(\bar{R}_0^{inf}(\lambda_1)-1)(\mu+\gamma)(1-\eta)}{2\sigma}\right) \\ &\qquad \epsilon_1\exp[\lambda_1(\tau_0-kLT)], \\ &\qquad \text{using Definition 5.2 and inequality (16),} \\ &= \left(\frac{(\bar{R}_0^{inf}(\lambda_1)+1)(\mu+\gamma)(1-\eta)}{2\sigma}\right)\epsilon_1\exp[\lambda_1(\tau_0-kLT)], \\ &= \frac{\mu+\gamma+\lambda_1}{\sigma}\frac{\mu+\sigma+\lambda_1}{\mu+\sigma}(1-\eta)\epsilon_1\exp[\lambda_1(\tau_0-kLT)], \\ &\qquad \text{using equation (14).} \end{aligned}$$

Since η is arbitrarily small, we can choose η small enough so that $(\mu+\sigma+\lambda_1)(1-\eta)/(\mu+\sigma) > 1$, and

$$E(t_0+\tau_0) > \frac{(\mu+\gamma+\lambda_1)}{\sigma}\epsilon_1\exp[\lambda_1(\tau_0-kLT)]. \tag{19}$$

Hence, (18) and (19) contradict (17); so we deduce that $\tau_0 = \infty$, and assuming that $I(\zeta)$ always lies below ϵ_0,

$$I(t_0+\tau) \geq \epsilon_1\exp[\lambda_1(\tau-kLT)] \text{ and } E(t_0+\tau) \geq \frac{(\mu+\gamma+\lambda_1)\epsilon_1}{\sigma}\exp[\lambda_1(\tau-kLT)],$$

for $\tau \geq 0$. In particular, $I(t)$ must rise again above its initial value ϵ_0 by a time at most $\tilde{T} = kLT + T_7 + \tau_1$, where $\tau_1 = (1/\lambda_1)\ln(\epsilon_0/\epsilon_1)$, and this time depends only ϵ_0, ψ, and the model parameters. Moreover, for all $t \geq 0$, we have that

$$I(t) \geq \eta_0 = \epsilon_0 \exp[-(\mu+\gamma)(kLT + T_7 + \tau_1)].$$

Next, suppose that $\epsilon_0 > I(0) > \eta_1 > 0$. A similar argument shows that provided $\eta_1 > 0$, $I(t)$ rises above ϵ_0 by a time at most $T(\eta_1) = kLT + T_7 + \tau_2$, which depends only on η_1 and the model parameters, not on the initial conditions, where $\tau_2 = (1/\lambda_1)\ln(\epsilon_0/\epsilon_2)$ and

$$0 < \epsilon_2 < \min\left\{\frac{\eta_1}{2}\exp[-(\mu+\gamma)(t_0+kLT)], \right.$$
$$\left. \frac{\sigma}{2(\mu+\gamma+\lambda_1)} E_1 \exp[-(\mu+\sigma)(t_0+kLT-T_4)]\right\}.$$

Moreover, by our previous argument, $I(t)$ remains above η_0 for $t \geq T(\eta_1)$. □

Hence, if $I(0) > \eta_1$, then $I(t) \geq \eta_0$ for all $t \geq T(\eta_1)$, where $T(\eta_1)$ depends only on η_1 and the model parameters. So, we can look for nonzero periodic solutions for our system when $R_0^{inf} > 1$. The following theorem gives the existence of a periodic solution of the system (1)–(5) with period LT.

THEOREM 5.2. *The system (1)–(5) has a nonzero LT-periodic solution.*

Proof The set $\mathbf{Z} = \mathcal{R}^4$ with the norm $|\mathbf{z}| = \sqrt{S^2+E^2+I^2+R^2}$ is a Banach space [3]. Defining the sets

$$L_0 = \left\{(S,E,I,R):\ S\geq 0,\ E\geq 0,\ I\geq \eta_0,\ R\geq 0,\ S+E+I+R=N\right\},$$
$$L_1 = \left\{(S,E,I,R):\ S\geq 0,\ E\geq 0,\ I> \frac{\eta_0}{2},\ R\geq 0,\ S+E+I+R=N\right\},$$
$$L_2 = \left\{(S,E,I,R):\ S\geq 0,\ E\geq 0,\ I\geq 0,\ R\geq 0,\ S+E+I+R=N\right\},$$

we find that L_0 and L_2 are compact, L_1 is open relative to L_2 (i.e., L_2-L_1 is closed), and L_0, L_1, and L_2 are convex sets.

Define the mapping $h : L_2 \to L_2$ such that

$$h(\mathbf{z}_0) = \mathbf{z}(LT,\ 0,\ \mathbf{z}_0).$$

Then $h(\mathbf{z}_0)$ is the solution of the initial value problem (1)–(5) at time LT with $\mathbf{z}_0 = (S(0),\ E(0), I(0), R(0))$ at time $t = 0$. The mapping h is continuous since the right-hand side of the system (1)–(5) is differentiable. Then for any positive integer j, the image of the set L_1 remains contained completely in the set L_2, so for $j = 1,\ 2,\ 3,\ \ldots$ we find that

$$h^j(L_1) \subset L_2.$$

Now suppose that $\mathbf{z}_0 \in L_1$. Then for $t \geq T(\frac{1}{2}\eta_0)$, $I(t) \geq \eta_0$. Hence, if $m_0 LT \geq T(\frac{1}{2}\eta_0)$, then we have $h^m(L_1) \subset L_0$ for all $m \geq m_0$. Then by Horn's Fixed Point Theorem [8], the mapping h has a fixed point in the set L_0. Hence, the system (1)–(5) has a nonzero LT-periodic solution. □

6. Persistence results.

6.1. Stability of the DFS when $R_0^{inf} > 1$.

Suppose first that $E(0) = I(0) = 0$. Then from equations (1)–(5), we find that $E(t) = I(t) = 0$ for all t. Arguing as in the proof of Theorem 4.1, we deduce that $(S(t), R(t)) \to (\hat{S}(t), \hat{R}(t))$ as $t \to \infty$, whatever the value of $R_0^{inf} > 1$.

Next, consider the case where $E(0) > 0$ or $I(0) > 0$. If $I(0) = 0$, then it is straightforward to show from (3) that $I(\Delta t) > 0$ for Δt small and positive. So, by changing the time origin, if necessary, we deduce the following from Theorem 5.1:

COROLLARY 6.1. *The DFS is unstable if* $R_0^{inf} > 1$.

6.2. Persistence of the disease when $R_0^{inf} > 1$.

Now we examine the persistence of the disease when $R_0^{inf} > 1$. Here, persistence means that the number of infectives is bounded away from zero.

DEFINITION 6.1. *For a function* $f : [0, \infty) \to \mathcal{R}^+$, *we define* $f_\infty = \liminf_{t\to\infty} f(t)$.

DEFINITION 6.2. Uniform strong repeller. *Following* [16], *we say that the set*

$$q = \{I = 0 : 0 \le S(t) \le N,\ 0 \le E(t) \le N,\ 0 \le S(t) + E(t) \le N\}$$

is a uniform strong repeller for the set

$$G = \{(S, I, E) : 0 \le S \le N,\ 0 < I \le N,\ 0 \le E \le N,\ 0 \le S + I + E \le N\},$$

if $I_\infty > 0$.

DEFINITION 6.3. Uniform persistence. *We say that the disease is uniformly persistent if each of* $S(t)$, $E(t)$, $I(t)$, *and* $R(t)$ *is strictly bounded away from zero, and moreover, this bound depends only on the model parameters.*

From Theorem 5.1, we have the following corollary.

COROLLARY 6.2. *If* $R_0^{inf} > 1$, *then the set* q *is a uniform strong repeller for the set* G.

Proof As $I_\infty \ge \eta_0$ the result is obvious. □

Our next step is to show that the disease is uniformly persistent when $R_0^{inf} > 1$. From Theorem 5.1, $I(t)$ is bounded away from zero for large times. We need to show that $S(t), E(t)$, and $R(t)$ are similarly bounded away from zero for large times.

LEMMA 6.1. $R_\infty \ge \eta_3 > 0$, *where* η_3 *depends only on the model parameters.*

Proof Given $\epsilon_1 > 0$, there exists t_1 such that $I(t) \ge \eta_0 - \epsilon_1$ for $t \ge t_1$. Then for $t \ge t_1$ from (4),

$$\frac{dR}{dt} \ \ge\ \mu Np + \gamma(\eta_0 - \epsilon_1) - (\mu + \delta)R.$$

Integrating this inequality and arguing as in Lemma 4.1, we deduce that

$$R_\infty \ \ge\ \frac{\mu Np + \gamma(\eta_0 - \epsilon_1)}{(\mu + \delta)}.$$

Letting $\eta_3 = (\mu Np + \gamma\eta_0)/(\mu + \delta)$, the result follows by letting $\epsilon_1 \to 0$. □

LEMMA 6.2. $S_\infty \ge \eta_4 > 0$, *where* η_4 *depends only on the model parameters.*

Proof Given $\epsilon_1 > 0$, there exists t_2 such that $R(t) \geq \frac{1}{2}\eta_3 - \epsilon_1$ for $t \geq t_2$. Then for $t \geq t_2$ from equation (1), we have that

$$\frac{dS}{dt} \;\geq\; \mu N(1-p) + \delta\left(\frac{1}{2}\eta_3 - \epsilon_1\right) - \left(\beta_{max}N + \mu + r_{max}\right) S.$$

Arguing as in Lemma 6.1, we deduce that

$$S_\infty \;\geq\; \eta_4 = \frac{\mu N(1-p) + \frac{1}{2}\delta\eta_3}{\beta_{max}N + \mu + r_{max}} > 0.$$

□

LEMMA 6.3. *The exposed population is bounded away from zero by a bound that depends only on the model parameters.*

Proof There exists t_3 such that for $t \geq t_3$, $S(t) \geq (S_\infty/\sqrt{2})$ and $I(t) \geq (I_\infty/\sqrt{2})$. Hence, for $t \geq t_3$ from (2),

$$\frac{dE}{dt} + (\mu+\sigma)E \quad\geq\quad \frac{1}{2}\beta(t)S_\infty I_\infty. \tag{20}$$

Choose n such that $nLT \geq t_3$ then multiply (20) by $\exp[(\mu+\sigma)t]$ and integrate

$$E((n+1)LT)\exp[(\mu+\sigma)(n+1)LT]$$
$$\geq E(\,nLT\,)\exp\left[(\mu+\sigma)nLT\right] + \frac{1}{2}S_\infty I_\infty \int_{nLT}^{(n+1)LT} \beta(t)\exp\left[(\mu\;+\;\sigma)t\right]dt.$$

So

$$E((n+1)LT) \geq\; \frac{1}{2}S_\infty I_\infty \int_0^{LT} \beta(t)\exp[(\mu+\sigma)(t-LT)]dt = \epsilon_1 > 0,$$

considering the fact that $\beta(t)$ is a nonzero, continuous, positive function so the integral is strictly positive. Moreover, ϵ_1 depends only on the model parameters. But

$$\frac{dE}{dt} \quad\geq\quad -(\mu+\sigma)E.$$

So for $(n+2)LT \geq t \geq (n+1)LT$,

$$E(t) \geq \epsilon_1 \exp\left[-(\mu+\sigma)(t-(n+1)LT)\right] \geq \epsilon_2 = \epsilon_1\exp[-(\mu+\sigma)LT].$$

Hence, $E(t) \geq \epsilon_2$ for all $t \geq (n+1)LT$. Lemma 6.3 follows. □

From Lemmas 6.1 through 6.3 and Theorem 5.1 we find that $\min\left(S_\infty, E_\infty, I_\infty, R_\infty\right) = c > 0$. So if $R_0^{inf} > 1$, then $S(t)$, $E(t)$, $I(t)$, and $R(t)$ are strictly bounded away from zero, and moreover, this bound depends only on the model parameters. Hence, the disease is uniformly persistent when $R_0^{inf} > 1$.

7. **Implications of results.** Our results for the SEIRS model with a periodic vaccination strategy are less complete than those for the corresponding SIRS model [10]. We have not been able to show that the disease will die out if $R_0^c \leq 1$ and that it will take off if $R_0^c > 1$. We have shown that the disease always dies out if $R_0^{sup} < 1$ and that if $R_0^{inf} > 1$ the DFS is unstable, the disease is uniformly persistent if initially present, and an LT-periodic solution exists. As the disease is uniformly persistent if initially present when $R_0^{inf} > 1$, we deduce that instability of the DFS when $R_0^{inf} > 1$ can be extended from not being locally asymptotically stable to being Lyapunov unstable.

It is straightforward from the definitions of R_0^{sup} and R_0^{inf} to show that

$$R_0^{max} = \frac{\sigma\beta_{max}\hat{S}_{max}}{(\mu+\sigma)(\mu+\gamma)} \geq R_0^{sup} \geq R_0^{inf} \geq R_0^{min} = \frac{\sigma\beta_{min}\hat{S}_{min}}{(\mu+\sigma)(\mu+\gamma)}.$$

Here, $\beta_{min} = \inf_{u\in[0,LT]} \beta(u)$, $\hat{S}_{max} = \sup_{u\in[0,LT]} \hat{S}(u)$, and $\hat{S}_{min} = \inf_{u\in[0,LT]} \hat{S}(u)$. Hence, if $R_0^{max} < 1$, then the disease will die out, and if $R_0^{min} > 1$, the DFS is unstable, the disease is uniformly persistent, and an LT-periodic solution exists.

We can also show that $R_0^{sup} \geq R_0^c \geq R_0^{inf}$ with both inequalities being strict if $\beta(t)\hat{S}(t)$ is nonconstant on $[0, LT]$. Define

$$Z(t) = \int_0^{LT} y(t-u)f(u)du,$$

where $y(t) = \beta(t)\hat{S}(t)$ and $f(u) = (\mu+\sigma)\exp[-(\mu+\sigma)u]/(1-\exp[-(\mu+\sigma)LT])$, $0 \leq u \leq LT$. By the definitions of R_0^c, R_0^{sup}, and R_0^{inf}, we need only to show that

$$\inf_{t\in[0,LT]} Z(t) \leq \frac{1}{LT}\int_0^{LT} y(\tau)d\tau \leq \sup_{t\in[0,LT]} Z(t),$$

with strict inequality if $y(t)$ is nonconstant. Now

$$\begin{aligned}
\int_0^{LT} Z(t)dt &= \int_0^{LT}\int_0^{LT} y(t-u)f(u)dudt, \\
&= \int_0^{LT}\int_{-u}^{LT-u} y(s)f(u)dsdu, \qquad \text{letting } s = t-u, \\
&= LT\overline{y}\int_0^{LT} f(u)du, \\
&= LT\overline{y}.
\end{aligned}$$

Hence, $\inf_{t\in[0,LT]} Z(t) \leq \overline{y} = \frac{1}{LT}\int_0^{LT} Z(t)dt \leq \sup_{t\in[0,LT]} Z(t)$, with both inequalities being strict unless $Z(t)$ is a constant. Write

$$\begin{aligned}
Z(t) &= \int_{t-LT}^{t} y(s)f(t-s)ds, \\
Z'(t) &= \int_{t-LT}^{t} y(s)f'(t-s)ds - y(t)(f(0)-f(LT)).
\end{aligned}$$

If $Z(t)$ is a constant, then $Z'(t) = 0$; so,

$$y(t) \;=\; \frac{(\mu+\sigma)}{(f(LT)-f(0))}Z(t)$$

is also a constant.

A sufficient condition for the DFS to be GAS is that $R_0^{sup} < 1$, equivalently

$$\sup_{t\in[0,LT]} \int_0^{LT} \frac{(\mu+\sigma)y(t-\zeta)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]} < \frac{(\mu+\sigma)(\mu+\gamma)}{\sigma}, \tag{21}$$

and a necessary condition is that $R_0^{inf} > 1$, equivalently

$$\inf_{t\in[0,LT]} \int_0^{LT} \frac{(\mu+\sigma)y(t-\zeta)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]} > \frac{(\mu+\sigma)(\mu+\gamma)}{\sigma}. \tag{22}$$

In the case that β is a constant, the first condition becomes

$$\sup_{t\in[0,LT]} \int_0^{LT} \frac{(\mu+\sigma)\hat{S}(t-\zeta)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]} < \frac{(\mu+\sigma)(\mu+\gamma)}{\sigma\beta}, \tag{23}$$

and the second

$$\inf_{t\in[0,LT]} \int_0^{LT} \frac{(\mu+\sigma)\hat{S}(t-\zeta)\exp[-(\mu+\sigma)\zeta]d\zeta}{1-\exp[-(\mu+\sigma)LT]} > \frac{(\mu+\sigma)(\mu+\gamma)}{\sigma\beta}. \tag{24}$$

We might conjecture that a necessary and sufficient condition for the DFS to be GAS is $R_0^c \le 1$, which is equivalent to

$$\frac{\int_0^{LT}\beta(\tau)\hat{S}(\tau)d\tau}{\int_0^{LT}\beta(\tau)d\tau} \;\le\; \frac{(\mu+\sigma)(\mu+\gamma)LT}{\int_0^{LT}\sigma\beta(\tau)d\tau} \;=\; \tilde{S}_c. \tag{25}$$

Condition (25) says that the average number of susceptibles in the DFS weighted by $\beta(t)$ over the period of the vaccination function is less than or equal to a critical value $\tilde{S}_c$.

Recall that a similar condition for local stability of the DFS, $\hat{S}(t)$, for $L = 1$,

$$\frac{\int_0^{T}\beta(\tau)\hat{S}(\tau)d\tau}{\int_0^{T}\beta(\tau)d\tau} \;<\; \frac{(\mu+\gamma)T}{\int_0^{T}\beta(\tau)d\tau} \;=\; S_c,$$

was obtained for a pulse vaccination function $r(t) = p\sum_{n=0}^{\infty}\delta(t-nT)$ by Shulgin et al. [15] in an SIR model. In the case that $\beta(t)$ is a constant and $L = 1$ condition (25) becomes

$$\frac{1}{T}\int_0^T \hat{S}(\tau)d\tau \;\le\; \frac{(\mu+\sigma)(\mu+\gamma)}{\sigma\beta}, \tag{26}$$

and Shulgin's condition

$$\frac{1}{T}\int_0^T \hat{S}(\tau)d\tau \;<\; \frac{(\mu+\gamma)}{\beta}.$$

8. **Summary and Discussion.** We have extended the work of [6] and [10] from SIRS epidemic models to the more realistic and complicated SEIRS model. It is important to include an exposed or latent class in our models, because many childhood diseases have a latent period. We have studied control of the dynamics of the infectious disease by using periodic vaccination of susceptibles of all ages, combined with immunization of a given proportion of newborns. We did this both for a constant and for a seasonally varying disease transmission rate. Using a

periodic vaccination strategy in such a SEIRS model seems to lead to periodicity in the disease dynamics.

This work can be summarized as follows. In section 1 a short introduction to common, practically used vaccination strategies was given. Section 2 outlined the SEIRS model that we studied and gave the assumptions underpinning the model. Section 3 showed that there is a unique DFS for our SEIRS epidemic model, and this solution is periodic with a period equal to that of the vaccination function. We also gave a conjectured expression for R_0, the basic reproduction number of the disease, when the vaccination campaign $r(t)$ is used. Lower and upper bounds, R_0^{inf} and R_0^{sup}, respectively, for this expression were also defined. In this section, we also studied the stability of the DFS of our model. We found that the DFS was GAS when $R_0^{sup} < 1$, and in this case, the infection will ultimately fade out of the population. In section 4, fixed-point theory was used to show the existence of nontrivial periodic solutions. Horn's Fixed Point Theorem showed that the model equations (1)–(5) have a nontrivial LT-periodic solution if $r(t)$ has period LT and $\beta(t)$ has period T.

Section 5 proved some persistence results when $R_0^{inf} > 1$. The DFS is unstable (neither locally asymptotically stable nor stable in the Lyapunov sense). When $R_0^{inf} > 1$, if the disease is present initially, it will persist and remain endemic in the population. We also showed that all of $S(t), E(t), I(t)$, and $R(t)$ were uniformly bounded away from zero. Finally, section 6 presented a conjecture for a condition under which an immunization program can prevent epidemics from occurring in the population. This is to keep a weighted mean value of the susceptible population at the DFS over the period of the vaccination function beneath a certain critical value. Our upper and lower bound results go some way toward proving this. A similar result for a SIRS model was found in [10]. We also gave an equivalent condition for $R_0^{sup} < 1$, that the maximum of a weighted average of the number of susceptibles at the DFS is less than a certain critical value, and a similar condition for $R_0^{inf} > 1$, that the minimum of the same weighted average exceeds the same critical value. The results were obtained for a SEIRS epidemic model with the disease transmission rate $\beta(t)$ having period T (or being a constant) and the vaccination function having period LT, where $L \geq 1$.

We conjectured that to control or eradicate the disease, it was both necessary and sufficient to keep the mean value of the product of the disease transmission rate and the susceptible population at the DFS beneath a critical threshold value. If this is true, then it is possible for sometimes only a few individuals to be vaccinated, provided only that the weighted mean value of the number of susceptibles at the DFS over the period of the vaccination function does not exceed the threshold value. The disease will still be eradicated. This contrasts with the strategy of constant vaccination, where a critical fixed level of immunization effort must always be applied to guarantee eradication, and this is an advantage of a periodic vaccination strategy over a constant one.

For a highly infectious disease such as measles, using vaccination at birth only requires that approximately 91% to 94% of newborn individuals be vaccinated to guarantee elimination of the disease [2]. It is difficult to achieve this level of vaccination coverage, particularly bearing in mind that measles vaccine efficacy is only around 95%, that some individuals may be difficult for health professionals to locate, and that others may refuse vaccination for religious or other reasons. Using a continuous periodic vaccination strategy in conjunction with vaccination of

a fixed proportion of newborn individuals reduces the proportion of newborns who need to be immunized to a more realistic level. Moreover, from (9), one can see easily that using such a mixed vaccination strategy uniformly reduces the level of fluctuation of susceptibles in the DFS compared with a purely periodic vaccination function ($p = 0$). Hence, it is more effective to use a combined vaccination approach to prevent major outbreaks of infectious disease from occurring.

9. **Appendix: List of symbols, abbreviations, and medical terms.**

$S(t)$: number of susceptibles at time t

$E(t)$: number of exposed individuals at time t

$I(t)$: number of infected individuals at time t

$R(t)$: number of removed individuals at time t

N: total population size

$\beta(t)$: total rate at which potentially infectious contacts occur between two individuals

$r(t)$: general continuous periodic vaccination strategy

T : period of contact rate

L: LT is period of vaccination function

$(1/\sigma)$: average latent period conditional on survival to the end of it

$(1/\delta)$: average immune period conditional on survival to the end of it

$(1/\gamma)$: average infectious period conditional on survival to the end of it

μ: common per capita birth and death rate

p: fraction of newborn children who are vaccinated

$\delta(t)$: Dirac delta function

R_0: basic reproduction number

R_0^c: conjectured value for basic reproduction number

R_0^{sup}: upper bound for R_0^c

R_0^{inf}: lower bound for R_0^c

$\tau = 1/(\mu + \gamma)$: average length of infectious period

DFS: disease-free solution

GAS: globally asymptotically stable

$\hat{S}(t)$: susceptible population at DFS

$\hat{R}(t)$: recovered population at DFS

E^∞: $\limsup_{t\to\infty} E(t)$

I^∞: $\limsup_{t\to\infty} I(t)$

REFERENCES

[1] Z. Agur, L. Cojocaru, G. Mazor, R. M. Anderson, and Y. Danon, Pulse mass measles vaccination across age cohorts. Proc. Natl. Acad. Sci. USA 90 (1993) 11698–702.

[2] R. M. Anderson and R. M. May, Infectious diseases of humans: Dynamics and control. Oxford University Press, Oxford, 1991.

[3] T. A. Burton, Stability and periodic solutions of ordinary and functional differential equations. Academic Press, New York, 1985.

[4] C. A. De Quadros, J. K. Andrus, and J. M. Olivé, Eradication of poliomyelitis: Progress. Am. Pediatr. Inf. Dis. J. 10 (1991) 222–9.

[5] K. Dietz, The incidence of infectious diseases under the influence of seasonal fluctuations. In Proceedings of a workshop on mathematical modelling in medicine, Mainz, ed. J. Berger, W. Bühler, R. Repges, and P. Tautu. Lecture Notes in Biomathematics 11. Springer-Verlag, Berlin, 1976, 1–15.

[6] D. Greenhalgh and I. A. Moneim, SIRS epidemic model and simulations using different types of seasonal contact rate. Syst. Anal. Mod. Simul. 43(5) (2003) 573–600.

[7] J. K. Hale, Ordinary differential equations. Wiley, New York, 1969.

[8] W. A. Horn, Some fixed point theorems for compact maps and flows in Banach spaces. Trans. Amer. Math. Soc. 149 (1970) 391–404.

[9] W. P. London and J. A. Yorke, Recurrent outbreaks of measles, chickenpox and mumps, I. Amer. J. Epidemiol. 98 (1973) 453–468.

[10] I. A. Moneim and D. Greenhalgh, Threshold and stability results for an SIRS epidemic model with a general periodic vaccination strategy. J. Biol. Systems. 13(2) (2005) 131–150.

[11] D. Nokes and J. Swinton, The control of childhood viral infections by pulse vaccination. IMA. J. Math. Appl. Med. Biol. 12 (1995), 29–53.

[12] S. C. Pannuti, J. C. Moraes, V. A. Souza, M. C. C. Camargo, and N. T. R. Hidalgo, Measles antibody prevalence after mass immunization in São-Paulo, Brazil. Bull. WHO 69 (1991) 557–60.

[13] A. B. Sabin, Measles, killer of millions in developing countries: Strategies of elimination and continuing control. Eur. J. Epidemiol. 7 (1991), 1–22.

[14] I. B. Schwartz and H. L. Smith, Infinite subharmonic bifurcations in an SEIR model. J. Math. Biol. 18 (1983), 233–53.

[15] B. Shulgin, L. Stone and Z. Agur, Pulse vaccination strategy in the SIR epidemic model. Bull. Math. Biol. 60 (1998), 1123–48.

[16] H. R. Thieme, Persistence under relaxed point-dissapitivity (with application to an endemic model). SIAM J. Math. Anal. 24 (1993), 407–35.

[17] P. J. Williams and H. F. Hull, Status of measles in The Gambia, 1981. Rev. Inf. Dis. 5 (1983) 391–394.

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